REMARKS

Applicants appreciate the thorough examination of the present application as evidenced by the final Office Action dated February 24, 2004 (hereinafter, "Final Action").

Claims 1-19 are pending in the present application. Claims 1-19 stand rejected under 35 U.S.C. § 103. The issues presented in the Final Action are addressed below.

I. Claim Objections

Applicants appreciate the indication that the objection to Claim 14 has been withdrawn in view of Applicant's amendment of Claim 14.

II. Claim Rejections Under 35 U.S.C. § 103

Claims 1-19 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over WO 96/05846 to Nebe (Nebe), U.S. Patent No. 5,696,236 to Omar et al. (Omar et al.) and EP 0798003A2 to Savage et al. (Savage et al.) for reasons of record. In particular, the Final Action states that "one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references." Final Action, page 2. Applicants agree with this assertion; however, it is the **combination** of the cited references that fail to teach or suggest the present invention as recited in the pending claims. Applicants previously pointed to the deficiency of each reference and further noted that these deficiencies are not cured by any of the other references.

Turning to the specific issues raised in the Final Action, the Final Action states that "Applicant's specification has not defined the term "removal" to be a complete elimination of the infectious agent. . . . Therefore, applicant's arguments are not convincing because the Nebe reference clearly sets out method steps comprising the use of a pre-filter which results in the removal of prion protein from the solution." Final Action, page 3. Claim 1 recites as follows:

> A method of removal of abnormal infective prion proteins associated with transmissible spongiform encephalopies (TSEs) from an aqueous liquid containing a natural product, which comprises passing the liquid through a **depth filter formed of a matrix comprising solid particles of porous material and having a pore size providing a retention less than 6 μm, and so removing any**

abnormal infective prion proteins which may be present in the liquid. (emphasis added).

Applicants respectfully submit that at least the highlighted portions of Claim 1 are not disclosed by the cited references. Focusing on "removal," Claim 1 specifically recites that "any abnormal infective prion proteins which may be present in the liquid" is removed. The examples of the present application show that there is **no detectable prion protein in the filtrate after filtration** according to the methods of the present invention. The examples further show that other types of filters, such as those employed in some of the cited references, were not effective in removing prion proteins. Results are summarized in Table 1 on page 14 of the specification.

In stark contrast, Nebe shows that the pre-filter removed only half of the infectious agent enabling the liquid to transmit prion protein disease to the patient. The filters employed by Nebe were **not effective** in removing prion proteins, where nearly five logs of infectivity/ml passed through the filters as shown on page 13 of Nebe. Applicants previously provided an unofficial translation of portions of Nebe for the purpose of responding to the Office Action dated July 15, 2003 and have also attached a copy herewith for the convenience of the Examiner. A review of the data indicates that the titre of the infectious scrapie material was $10^{8.45}$ LD50/ml. *See* unofficial translation of Nebe, Example 1, Section 1.3, last paragraph). 10 ml of the scrapie spike was added to 600 ml of the thymus homogenate (*see* unofficial translation of Nebe, Example 1, Section 1.3, first paragraph) which provided a starting level of infectivity of $10^{6.66}$ LD50/ml. Figure 1 of Nebe, right of the flow chart, shows a "reduction" in infectivity of only $10^{1.23}$. Thus, the final infectivity is approximately $10^{5.4}$. This correlates approximately with the figure of $10^{4.97}$ given as the infectivity of Probe A. Consequently, there is a minimal reduction in infectivity of 1.23 logs/ml leaving a high residual infectivity of about 5 logs/ml.

Again, the examples of the present application show that there is **no detectable prion protein in the filtrate after filtration** according to the methods of the present invention. Claim 1 recites that the methods of the present invention removes "any abnormal infective prion proteins which may be present in the liquid." Consequently, it is clear that Nebe does not teach or suggest a method of removal of

abnormal infective prion proteins from an aqueous liquid which, among other things, removes **any** abnormal infective prion proteins **which may be present in the liquid**.

The Final Action cites Omar et al. and Savage et al. to cure the deficiencies of Nebe. In particular, the Final Action states that Omar et al. "teaches separating virus from protein solution using an absorbent (binder) that is either diatomaceous earth, perlite or kieselguhr," (Final Action, page 3) and Savage et al. "teach a method of removal of viruses from an aqueous liquid containing proteins, the method comprises the steps of passing the liquid through a depth filter formed of matrix comprising porous elements having a size 0.25-2 microns" (Final Action, page 4). Applicants respectfully submit that neither Omar et al. nor Savage et al. cure the deficiencies of Nebe.

Both Omar et al. and Savage et al. are concerned with the removal of viruses and not prion proteins. Omar et al. discusses a method for the removal of **viruses** from protein solutions. *See* Col. 1, lines1-2. Savage et al. discusses removing **viruses** from solutions. *See* page 5, line 5. As noted in the present application on page 2, paragraph 1 through page 3, paragraph 1, prions are known to be abnormal proteins having infectious capacity. While viruses also have infectious capacity, the virus infection is governed by a completely different mechanism than prion infection as noted in Flint et al., *Principles of Virology: Molecular Biology, Pathogenesis, and Control*, ASM Press, **15-17** (2000), and Riesner, "Biochemistry and structure of PRP^{C} and PrP^{Sc}," *British Medical Bulletin* **66:21-33** (2003) (copies attached herewith). Thus, Applicants respectfully submit that one of ordinary skill in the art would not rely upon Savage et al. and/or Omar et al. to address the problem of improving the **ineffective prion removal rate** disclosed in Nebe.

Accordingly, Applicants respectfully submit that the rejection of Claim 1, and Claims 2-16 dependent therefrom, should be withdrawn for at least these reasons. For similar reasons as discussed above, Applicants respectfully submit that the rejection of amended Claim 17, amended Claim 18 and Claim 19 should also be withdrawn.

III. New Claims 20-23

Applicants have added new Claims 20-23. Support for these new claims can be found in the specification at page 4, paragraph 4 through page 5 and page 5, paragraphs 2 and 4, among other places. Accordingly, Applicants respectfully submit that no new matter is added by the entry of new Claims 20-23, and respectfully request entry thereof.

Additionally, new Claims 20-23 are asserted to be patentable over the combination of Nebe, Omar et al. and Savage et al. for at least the reasons discussed below. The cited references neither alone nor in combination provide a method of removal of abnormal infective prion proteins wherein abnormal infective prion proteins are completely removed and the liquid is non-infective with respect to prion protein infectivity as recited in new Claim 20. The cited references neither alone nor in combination provide a method of removal of abnormal infective prion proteins wherein the removal of abnormal infective prion proteins is achieved to an extent of at least 10^3 as recited in Claim 21. The cited references neither alone nor in combination provide a method of removal of abnormal infective prion proteins wherein the removal of the abnormal infective prion proteins is achieved to an extent of at least 10^4 as recited in Claim 22. Finally, the cited references neither alone nor in combination provide a method wherein the filter is a single use filter as recited in Claim 23. Accordingly, Applicants respectfully submit that new Claims 20-23 are allowable over the cited references for at least these reasons.

Conclusion

Applicants respectfully submit that, for the reasons discussed above, the references cited in the present rejection do not disclose or suggest the present invention as claimed. Accordingly, Applicants respectfully request allowance of all the pending claims and passing this application to issue. The Examiner is invited and encouraged to contact the undersigned directly if such contact will expedite the prosecution of the pending claims to issue. In any event, any questions that the Examiner may have should be directed to the undersigned, who may be reached at (919) 854-1400.

It is not believed that any fee(s), including fees for additional claims, are required, beyond those that may otherwise be provided for in documents accompanying this paper. In the event, however, that additional fees are necessary to allow consideration of this paper, such an extension is also hereby petitioned for under 37 C.F.R. §1.136(a). Applicants authorize that any additional fees believed to be due in connection with this paper may be charged to Deposit Account No. 50-0220.

Respectfully submitted,

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Susan E. Freedman
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